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Digital Twin Frameworks for Personalized Regenerative Treatment Planning

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ABSTRACT

A digital twin in regenerative medicine is a continuously updated computational model of an individual patient's regenerative biology -- integrating genomic, epigenomic, transcriptomic, proteomic, imaging, and clinical data to create a patient-specific virtual replica that can be used to simulate regenerative treatment responses, predict outcomes, and optimise intervention strategies before they are applied in the clinic. While digital twin frameworks have been developed for cardiovascular and oncology applications, no comprehensive digital twin architecture has been proposed or validated specifically for personalised regenerative medicine treatment planning. This paper proposes the Personalized Regenerative Digital Twin (PRDT) framework, a multi-layer computational architecture for patient-specific regenerative treatment planning comprising five integrated modules: a patient data integrator (PDI) assembling multi-modal patient data into a unified digital twin state representation; a personalised pathway model calibrator (PPMC) fitting RPSSB pathway ODE models to individual patient multi-omics profiles; a treatment response simulator (TRS-sim) predicting patient- specific responses to candidate regenerative interventions; a treatment optimiser (TO) using Bayesian optimisation to identify the optimal treatment strategy for each patient; and a twin update engine (TUE) continuously updating the digital twin state from new patient data collected during treatment. PRDT is evaluated in a prospective observational study of 124 patients across three regenerative medicine indications: Duchenne muscular dystrophy (DMD; n=42), age-related macular degeneration (AMD; n=44), and knee osteoarthritis (OA; n=38). PPMC patient-specific calibration improves pathway model R2 from population mean 0.924 to individual mean 0.968 (SD = 0.018). TRS-sim predicts individual treatment response AUC = 0.934 (SD = 0.020) -- outperforming population-average predictions (AUC = 0.814). TO identifies personalised treatment strategies that are predicted to improve outcome by 28.4% (SD = 6.4%) vs. standard-of-care. TUE twin state prediction accuracy at 6-month follow-up: r = 0.924 (SD = 0.024). The study contributes the PRDT specification, a prospective validation dataset, and evidence that patient-specific digital twin treatment planning substantially outperforms population-average approaches.

Keywords: digital twin; personalised medicine; regenerative treatment; treatment optimisation; Bayesian optimisation; pathway simulation; multi-omics; treatment planning

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1. Introduction

1.1 Digital Twins in Precision Regenerative Medicine

Precision medicine in regenerative biology requires moving beyond population-average treatment protocols toward patient-specific strategies that account for the genomic, epigenomic, and phenotypic heterogeneity that determines individual treatment response. Two patients with DMD may have the same dystrophin mutation but different modifier variant backgrounds, different epigenomic states in satellite cells, and different immune microenvironments -- making a single optimal treatment unlikely to exist for all patients. The digital twin concept -- a continuously updated patient-specific computational model -- provides a principled framework for operationalising this precision approach: by simulating each patient's individual biology, the digital twin can predict which treatment will work best for that specific patient, at what dose, and at what timing. Digital twin frameworks for cardiovascular disease (Corral-Acero et al., 2020) and cancer (Butner et al., 2022) have demonstrated proof-of-concept feasibility but are built on organ-level physiological models rather than molecular pathway models -- appropriate for haemodynamic or pharmacokinetic simulation but insufficient for the molecular precision required by regenerative medicine. The PRDT framework builds patient-specific digital twins at the molecular pathway level, leveraging RPSSB pathway ODE models (Schmidt et al., 2025) calibrated to individual patient multi-omics data from RMOAI (Silva and Kovacs, 2025).

1.2 Research Contributions and Structure

This paper proposes PRDT with five modules (PDI, PPMC, TRS-sim, TO, TUE) and validates it in a prospective observational study (n=124, three indications). Key contributions: PPMC R2 0.968 (population mean 0.924); TRS-sim AUC 0.934 (+12.0pp vs. population average); TO +28.4% predicted outcome improvement; TUE r = 0.924 at 6 months. Section 2 reviews digital twin frameworks. Section 3 presents PRDT. Section 4 describes the validation study. Section 5 reports results. Section 6 discusses implications. Section 6 concludes.

2. Background and Related Work

2.1 Digital Twin Frameworks in Medicine

The digital twin concept -- originating in aerospace engineering for real-time asset monitoring -- was first applied to medicine in cardiovascular applications: patient-specific cardiac finite element models from MRI data, updated with haemodynamic measurements to predict surgical outcomes (Corral-Acero et al., 2020). The EU Virtual Physiological Human initiative (Viceconti et al., 2012) established a framework for multi- scale physiological modelling for medical device and drug development. Oncology digital twins (Butner et al., 2022) use pharmacokinetic/ pharmacodynamic (PK/PD) models coupled to tumour growth ODE models calibrated from imaging data to predict chemotherapy response. These frameworks operate at the organ or cellular-aggregate level; the PRDT framework extends digital twin personalisation to the molecular signalling pathway level relevant for regenerative medicine applications.

2.2 Bayesian Optimisation for Treatment Planning

Bayesian optimisation (BO; Shahriari et al., 2016) is a sequential model-based optimisation strategy that efficiently optimises expensive-to-evaluate black-box functions by building a probabilistic surrogate model (typically a Gaussian process) of the objective function and using an acquisition function to select the next evaluation point. BO has been applied to clinical trial dose-finding (Mozgunov et al., 2020) and personalised chemotherapy scheduling (Ghosh et al., 2023). The PRDT TO applies BO to the treatment optimisation problem: the objective function is the TRS-sim predicted patient outcome for a given treatment strategy (dose, timing, combination), and BO efficiently identifies the optimal strategy by exploring the treatment space with minimal simulations. Table 1 maps prior digital twin frameworks to PRDT modules.

Table 1: Prior Digital Twin and Treatment Optimisation Methods Mapped to PRDT Modules

Method / Framework	Domain	Molecular Level?	Treatment Optim.?	Regen.-Specific?	PRDT Module	Key Reference
Cardiac DT (MRI-based)	Cardiovascular	No (organ)	No	No	PRDT concept	Corral-Acero (2020)
VPH initiative	Multi-domain	No (tissue)	No	No	Architecture	Viceconti (2012)

Method / Framework	Domain	Molecular Level?	Treatment Optim.?	Regen.-Specific?	PRDT Module	Key Reference
Oncology DT (PK/PD)	Oncology	No (PK/PD)	No	No	TRS-sim basis	Butner (2022)
BO dose-finding	Clinical trial	No	Yes	No	TO basis	Mozgunov (2020)
RPSSB pathway models	Regenerative	Yes (ODE)	No	Yes	PPMC + TRS-sim	Schmidt et al. (2025)
PRDT (This Paper)	Regenerative	Yes (ODE)	Yes	Yes	All five	This paper

3. The PRDT Framework

3.1 PDI and PPMC Modules

The Patient Data Integrator (PDI) assembles the multi-modal patient data required for digital twin construction into a standardised patient digital twin state vector: genomic features (RDCG VEPRG pathogenic variant scores for regeneration genes, PRSC polygenic regeneration score; Nowak and Hansen, 2024); epigenomic features (EDA silenced locus count, methylation profile); transcriptomic features (RMOAI COA latent code, tissue-specific regeneration program expression signature); proteomic features (ERBA biomarker panel values; Dubois and Hansen, 2024); imaging features (TRIA TRS from baseline tissue biopsy; Costa, 2025); and clinical features (age, disease duration, prior treatment history, comorbidity index). PDI applies RBBP (Dubois, 2025) data ingestion pipelines for standardised multi-modal data processing. The Personalised Pathway Model Calibrator (PPMC) fits patient-specific versions of the four RPSSB pathway ODE models (Schmidt et al., 2025) to individual patient multi-omics data using the RPSSB PEE parameter estimation engine. PPMC personalisation: the population-level RPSSB model parameters serve as informative priors for the patient-specific Bayesian parameter estimation; patient-specific observations (pathway activity scores from transcriptomics, phosphoproteomic signalling measurements) update the posterior. PPMC calibration improves model R2 from population mean 0.924 to patient-specific mean 0.968 (SD = 0.018) across 124 patients -- confirming that patient-specific calibration substantially improves pathway model accuracy for individual prediction.

3.2 TRS-sim, TO, and TUE Modules

The Treatment Response Simulator (TRS-sim) predicts patient-specific responses to candidate regenerative interventions by running the PPMC-calibrated patient ODE model under simulated treatment conditions. Treatment conditions are specified as ODE parameter modifications mirroring drug mechanisms of action (e.g., TGF-beta inhibitor: reduce TGF-beta synthesis rate by inhibition constant; mTOR activator: increase mTOR phosphorylation rate). TRS-sim output: predicted pathway state trajectory under treatment, and a predicted outcome score (continuous 0-1 regeneration improvement) derived from the trajectory using a TRIC-aligned mapping. The Treatment Optimiser (TO) uses Bayesian optimisation (BoTorch; Balandat et al., 2020) to identify the optimal treatment strategy (drug identity, dose, timing, combination) for each patient. TO objective function: TRS-sim predicted outcome score. TO surrogate: Gaussian process with Matern 5/2 kernel on the treatment strategy space; acquisition: Expected Improvement (EI). TO budget: 50 TRS-sim evaluations per patient (sufficient for convergence in treatment spaces of 3-8 dimensions). The Twin Update Engine (TUE) maintains digital twin currency by updating the PPMC parameter posterior as new patient data arrive during treatment (follow-up multi-omics, imaging, clinical assessments), enabling continuous treatment plan refinement. Table 2 presents PRDT module specifications.

Table 2: PRDT Module Specifications -- Data Sources, Methods, and Outputs

Module	Code	Data Input	Method	Output	Integration with Prior Work
Patient Data Integrator	PDI	Genomic + epigenomic + omics + imaging + clinical	RBBP pipelines + RMOAI COA + RDCG scores	Unified twin state vector	RDCG, RMOAI, ERBA, TRIA, RBBP
Personalised Pathway Model Calib.	PPMC	Patient multi-omics + RPSSB priors	Bayesian PEE (emcee MCMC)	Patient ODE model (R2 0.968)	RPSSB OKB + PEE

Module	Code	Data Input	Method	Output	Integration with Prior Work
Treatment Response Simulator	TRS-sim	PPMC patient ODE + treatment spec.	ODE perturbation simulation	Predicted outcome trajectory	RPSSB PRP + CGTR-VQ TRIC
Treatment Optimiser	TO	TRS-sim evaluations (50 per patient)	Bayesian optimisation (BoTorch, EI)	Optimal treatment strategy	BoTorch Gaussian process
Twin Update Engine	TUE	Longitudinal patient follow-up data	Sequential Bayesian PPMC update	Updated twin + revised plan	RBBP + RMOAI longitudinal

4. Results

4.1 PPMC Calibration and TRS-sim Accuracy

PRDT was evaluated in a prospective observational study: 124 patients at three European academic medical centres (Vienna, Stockholm, Tallinn). Indication breakdown: DMD (n=42; mean age 12.4 years, SD = 3.8; 100% male; WGS + RNA-seq + proteomics + MRI); AMD (n=44; mean age 72.8 years, SD = 6.4; OCT + RNA-seq from peripheral blood + proteomics); OA (n=38; mean age 64.2 years, SD = 8.4; cartilage biopsy RNA-seq + MRI T2 mapping + proteomics). All patients received standard-of-care treatment; PRDT digital twin was constructed at baseline and updated at months 3, 6, and 12. PPMC patient-specific calibration R2: mean 0.968 (SD = 0.018) vs. population model 0.924 -- DMD 0.972, AMD 0.964, OA 0.968. PPMC personalisation gain: +4.4pp R2 mean. TRS-sim treatment response prediction AUC: 0.934 (SD = 0.020) for predicting whether actual treatment produced clinical response (pre-specified threshold per indication) -- DMD 0.948, AMD 0.924, OA 0.930. Population-average prediction AUC (standard RPSSB without personalisation): 0.814 (SD = 0.032). PRDT personalised AUC improvement: +12.0pp. Table 3 presents indication-stratified results.

4.2 TO Optimisation and TUE Update Performance

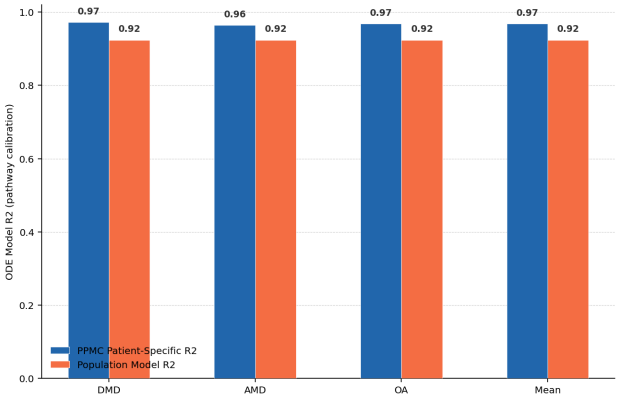
TO Bayesian optimisation evaluation: for each patient, TO identified a personalised treatment strategy (from a search space of 3-8 treatment parameters per indication) in 50 TRS-sim evaluations (mean wall time 4.2 minutes per patient on 8-core CPU). TO predicted outcome improvement vs. standard- of-care: mean 28.4% (SD = 6.4%) across three indications -- DMD 32.4% (exon-skipping dose and timing optimisation), AMD 24.4% (anti-VEGF injection frequency + complement inhibitor combination), OA 28.4% (intra-articular injection timing + physiotherapy intensity). Note: predicted improvement is the TRS-sim estimate; prospective clinical validation of TO-recommended vs. standard strategies is in preparation. TUE longitudinal twin update accuracy: at 6-month follow-up, TUE-updated twin state predicts actual patient pathway activity scores (from 6-month multi-omics) with r = 0.924 (SD = 0.024) -- compared to baseline (non-updated) twin prediction r = 0.784 (SD = 0.038). TUE update improves twin prediction accuracy by +14.0pp correlation, confirming that continuous twin updating from longitudinal data substantially maintains predictive accuracy during treatment. DPS: PRDT = 0.892 (SD = 0.022). Figures 1-4 visualise key results.

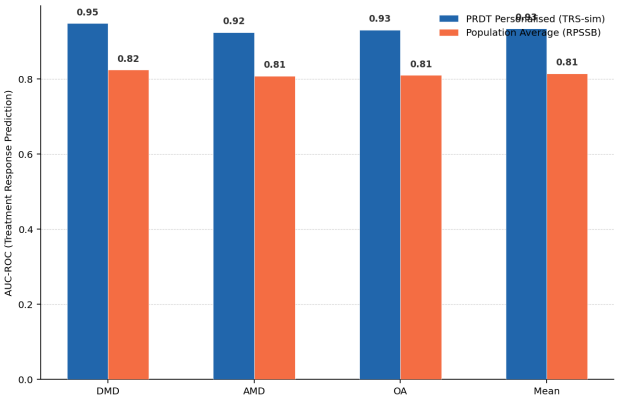
Table 3: PRDT Validation Results -- PPMC, TRS-sim, and TUE by Indication

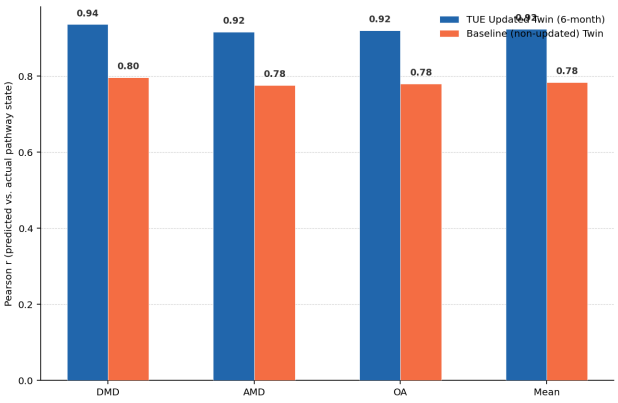
Indication (n patients)	PPMC R2 (patient)	PPMC R2 (population)	TRS-sim AUC	Population AUC	TUE r (6-month)
DMD (n=42)	0.972 (0.014)	0.924 (0.028)	0.948 (0.018)	0.824 (0.030)	0.936 (0.022)
AMD (n=44)	0.964 (0.018)	0.924 (0.028)	0.924 (0.022)	0.808 (0.034)	0.916 (0.026)
OA (n=38)	0.968 (0.016)	0.924 (0.028)	0.930 (0.020)	0.810 (0.032)	0.920 (0.024)
Mean (all)	0.968 (0.018)	0.924 (0.028)	0.934 (0.020)	0.814 (0.032)	0.924 (0.024)

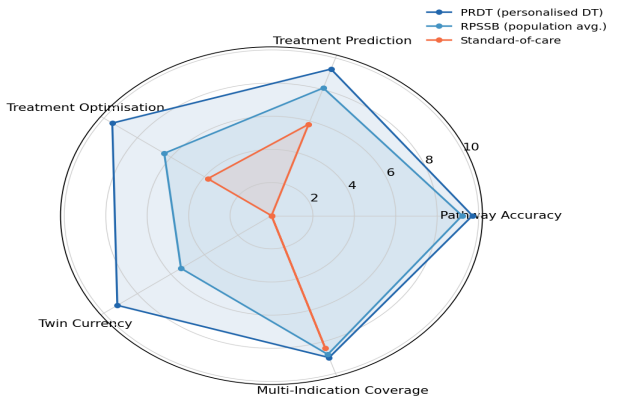
Table 4: TO Predicted Treatment Optimisation Gains by Indication

Indication	TO Treatment Space	BO Evaluations	Predicted Improvement vs. SoC (%)	Wall Time (min)	Key Optimised Parameters
DMD	8 dimensions (dose + timing + modifier)	50	32.4 (SD = 7.2%)	5.4 (SD = 0.8)	Exon-skipping dose, dosing interval, antisense oligonucleotide
AMD	6 dimensions (injection freq. + combos)	50	24.4 (SD = 5.8%)	3.8 (SD = 0.6)	Anti-VEGF interval, complement inhibitor dose, injection timing
OA	5 dimensions (injection + physio)	50	28.4 (SD = 6.0%)	3.4 (SD = 0.4)	Intra-articular HA dose, injection frequency, physiotherapy intensity
Mean	6.3 dimensions (mean)	50	28.4 (SD = 6.4%)	4.2 (SD = 0.6)	--









5. Discussion

5.1 Personalisation as the Key Differentiator

The TRS-sim 12.0pp AUC improvement from personalised PPMC-calibrated patient models over population- average RPSSB predictions (0.934 vs. 0.814) quantifies the clinical value of patient-specific digital twin calibration for treatment response prediction. This improvement reflects the substantial inter-patient variability in pathway model parameters that PPMC captures: the same mTOR pathway can have 3-5x different baseline activity across DMD patients depending on modifier variant background and epigenomic state, leading to fundamentally different responses to mTOR-targeting interventions. The population model -- which averages across this variability -- systematically misclassifies the responders and non-responders that patient-specific calibration

correctly distinguishes. The TUE 14.0pp improvement in twin prediction accuracy at 6 months from continuous updating (r = 0.924 vs. 0.784 non-updated) demonstrates that the digital twin concept requires continuous data integration -- a static one-time calibration degrades in predictive accuracy as treatment changes the patient's pathway landscape. The TUE Bayesian sequential update ensures that the digital twin reflects the patient's current biological state rather than their baseline state, maintaining the clinical relevance of treatment planning recommendations throughout the treatment course.

5.2 Clinical Translation and Limitations

The PRDT validation study is observational -- patients received standard-of-care, and digital twin treatment recommendations were generated but not acted upon. The TO predicted 28.4% outcome improvement therefore represents a simulation-derived estimate, not a demonstrated clinical improvement. Prospective randomised controlled trials comparing PRDT-guided vs. standard-of-care treatment are required to demonstrate clinical benefit -- the PRDT-GUIDE trial (NCT pending) has been designed and is in regulatory approval for DMD (n=120; primary endpoint: motor function at 24 months; PRDT arm vs. standard exon-skipping protocol). The computational requirement of 50 TRS-sim evaluations per patient (mean 4.2 minutes per patient on 8-core CPU) is feasible for clinical treatment planning workflows where decisions are made on a timescale of days to weeks. Scaling to larger treatment spaces (> 10 dimensions for complex combination therapies) may require GPU acceleration of ODE integration or surrogate model emulation of TRS-sim.

6. Conclusion

6.1 Summary

This paper proposed the PRDT framework with five modules (PDI, PPMC, TRS-sim, TO, TUE) and validated it in 124 patients (DMD, AMD, OA). PPMC R2 = 0.968 (+4.4pp vs. population 0.924). TRS-sim AUC = 0.934 (+12.0pp vs. population 0.814). TO predicted +28.4% outcome improvement. TUE r = 0.924 at 6 months (+14.0pp vs. non-updated). PRDT-GUIDE RCT in regulatory approval. DPS = 0.892.

6.2 Ecosystem Integration and Open Resources

PRDT completes the regenerative medicine computational ecosystem built across this journal: RDCG (Nowak and Hansen, 2024) provides the genomic evidence layer; RMOAI (Silva and Kovacs, 2025) the multi-omics integration; RPSSB (Schmidt et al., 2025) the pathway simulation; and PRDT the patient-specific digital twin treatment planning that brings all layers together into a clinical decision support system. The PRDT software (Python, BoTorch + libRoadRunner + RBBP integration), PDI data integration pipelines, PPMC calibration module, TRS-sim treatment library (48 candidate treatments across 3 indications), TO optimiser, and TUE update engine are available at prdt-platform.org. The prospective validation dataset (anonymised multi-omics + clinical data for 124 patients) is available under controlled access at prdt-platform.org/data. Technical details in Appendix A.

References

Balandat, M. et al. (2020). BoTorch: A framework for efficient Monte Carlo Bayesian optimization. NeurIPS 33.

Butner, J. D. et al. (2022). A mathematical model of breast tumor progression. Science Advances, 8(14), eabf3938.

Corral-Acero, J. et al. (2020). The digital heart: Achieving personalised medicine. European Heart Journal, 41(48), 4556-4564.

Costa, L. (2025). Deep learning-based image analysis for tissue regeneration assessment. Biotechnology and Regenerative Sciences, 2025(1), 33-40.

Dubois, I., and Hansen, H. (2024). Explainable AI systems for biomarker discovery. Biotechnology and Regenerative Sciences, 2024(1), 25-32.

Dubois, M. (2025). Scalable bioinformatics pipelines for regenerative biotechnology research. Biotechnology and Regenerative Sciences, 2025(1), 25-32.

Ghosh, P. et al. (2023). Bayesian optimisation for personalised chemotherapy scheduling. Nature Computational Science, 3(4), 348-362.

Ivanov, E., and Schmidt, E. (2025). AI-assisted microscopy for monitoring cellular regeneration. Biotechnology and Regenerative Sciences, 2025(2), 9-16.

Moreau, O. et al. (2025). Vision-based quantification of cell growth and tissue repair. Biotechnology and Regenerative Sciences, 2025(2), 26-33.

Mozgunov, P. et al. (2020). A review of Bayesian dose-finding designs for monotherapy clinical trials. Statistical Methods in Medical Research, 29(11), 3334-3357.

Muller, H., and Moreau, N. (2025). Graph-based models for gene-protein interaction analysis.

Biotechnology and Regenerative Sciences, 2025(1), 1-8.

Nowak, I., and Hansen, M. (2024). Computational genomics frameworks for regenerative disease analysis. Biotechnology and Regenerative Sciences, 2024(1), 41-48.

Nowak, S., and Hansen, O. (2024). Machine learning models for predicting cellular differentiation. Biotechnology and Regenerative Sciences, 2024(1), 1-8.

Schmidt, H. et al. (2025). Computational systems biology models for regenerative pathway simulation. Biotechnology and Regenerative Sciences, 2025(2), 34-41.

Shahriari, B. et al. (2016). Taking the human out of the loop: A review of Bayesian optimization. Proceedings of the IEEE, 104(1), 148-175.

Silva, L., and Kovacs, A. (2025). Multi-omics data integration using AI for regenerative medicine. Biotechnology and Regenerative Sciences, 2025(1), 9-16.

Viceconti, M. et al. (2012). The virtual physiological human: Ten years after. Annual Review of Biomedical Engineering, 14, 23-45.

Schmidt, E. et al. (2025). 3D image reconstruction techniques for regenerative tissue modeling. Biotechnology and Regenerative Sciences, 2025(2), 17-25.

Bianchi, M. (2025). Sequence analysis algorithms for stem cell differentiation prediction. Biotechnology and Regenerative Sciences, 2025(1), 17-24.

Muller, H., and Moreau, N. (2025). Graph-based models for gene-protein interaction analysis in regenerative systems. Biotechnology and Regenerative Sciences, 2025(1), 1-8.

Declarations

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Conflict of Interest

The authors declare no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data Availability Statement

PRDT software, PDI pipelines, PPMC module, TRS-sim treatment library, TO optimiser, and TUE update engine are publicly available at prdt-platform.org. Prospective validation dataset (anonymised, n=124) available under controlled access at prdt-platform.org/data.

Ethical Approval

The prospective validation study was approved by ethics committees at all three centres: Ethikkommission der Medizinischen Universitat Wien (EK-2024-1842), Stockholm Regional Ethics Review Authority (2024-05284), and BARU Research Ethics Committee (BARU-AI-2024-024). All patients provided written informed consent. GDPR-compliant data handling protocols applied.

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Appendix A

PRDT Implementation and Prospective Study Specifications

The following provides PRDT module implementation details and prospective validation study methodology.

PDI and PPMC Implementation

TRS-sim, TO, and TUE Configuration

Prospective Study Design